Emtricitabine/Tenofovir disoproxil fumarate

Brand Name: Truvada
Drug Class: Nucleoside Reverse Transcriptase Inhibitors

Drug Description

Truvada is a fixed-dose tablet containing two synthetic nucleoside analogues: emtricitabine and tenofovir disoproxil fumarate. Each tablet contains 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate. [1]

HIV/AIDS-Related Uses

Truvada (Emtricitabine/tenofovir disoproxil fumarate) was approved by the FDA on August 2, 2004, for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.[2] [3]

The approval of Truvada is based on safety and efficacy data that exist for both components individually and on bioequivalence studies demonstrating similar pharmacokinetic parameters of the combination product and the individual products. Efficacy results from studies using the combination of tenofovir and lamivudine are being extrapolated to support the use of Truvada. Truvada should be considered as an alternative to tenofovir and lamivudine for treatment-naive patients who might benefit from a once-a-day regimen.[4]

Pharmacology

Emtricitabine and tenofovir disoproxil fumarate each inhibit viral reverse transcriptase (RT), an enzyme HIV requires in order to replicate, by incorporating into viral DNA and terminating the viral DNA chain. (For more information, see the individual drug records for emtricitabine and tenofovir disoproxil fumarate.)

Emtricitabine, a synthetic nucleoside analogue of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate and by incorporating into nascent viral DNA, which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerases alpha, beta, and epsilon and of mitochondrial DNA polymerase gamma.[5]

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir disphosphate. Tenofovir disphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and by incorporating into DNA, which results in chain termination. Tenofovir disphosphate is a weak inhibitor of mammalian DNA polymerases alpha and beta and of mitochondrial DNA polymerase gamma.[6]

Administration of Truvada following a high fat meal or a light meal delayed the time of tenofovir peak plasma concentrations (Cmax) by approximately 0.75 hour. The mean increases in tenofovir area under the concentration-time curve (AUC) and Cmax were approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy studies, tenofovir disoproxil fumarate was taken under fed conditions. Emtricitabine AUC and Cmax were unaffected when Truvada was administered with either a high fat or a light meal.[7]

Emtricitabine is rapidly and extensively absorbed following oral administration, reaching Cmax at 1 to 2 hours post-dose. In one clinical trial, the mean absolute bioavailability of emtricitabine was 93% following multiple doses of the drug. The mean steady state Cmax was 1.8 mcg/ml and the AUC over a 24-hour dosing interval was 10.0 hr-mcg/ml. The mean steady state plasma trough concentration 24 hours after an oral dose was 0.09 mcg/ml.[8]

Emtricitabine is less than 4% bound to plasma proteins, and protein binding is independent of drug concentration over a range of 0.02 to 200 mcg/ml. In vitro studies indicate that emtricitabine does not inhibit CYP450 enzymes. Following administration of 14C-emtricitabine, the drug was 86% recovered in urine and 14% in feces. Thirteen percent of urine-recovered drug were metabolites, including 3'-sulfoxide diastereomers and 2'O-glucuronide; no other metabolites were identified. The plasma

Pharmacology (cont.)

half-life of emtricitabine is approximately 10 hours. Renal clearance of the drug exceeds estimated creatinine clearance, indicating elimination by glomerular filtration and tubular secretion. In patients with renal impairment, Cmax and AUC were increased.[9]

Oral bioavailability of tenofovir in fasted patients is approximately 25%. Administration of tenofovir with a high fat meal increases the oral bioavailability, with an increase in tenofovir AUC of approximately 40% and an increase in Cmax of approximately 14%. Food delays the time to tenofovir Cmax by approximately 1 hour. Following oral administration of a single 300 mg dose of tenofovir to HIV infected patients in the fasted state, Cmax is achieved in approximately 1.0 hour. Cmax and AUC values are approximately 0.296 mcg/ml and approximately 2.287 hr-mcg/ml, respectively. The pharmacokinetics of tenofovir are dose proportional over a wide dose range and are not affected by repeated dosing. In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7% and 7.2%, respectively, over the tenofovir concentration range of 0.01 to 25 mcg/ml. Following intravenous administration of tenofovir in doses of 1.0 mg/kg and 3.0 mg/kg, the volume of distribution at steady-state is 1.3 +/- 0.6 l/kg and 1.2 +/- 0.4 l/kg.[10]

In vitro studies indicate that neither tenofovir disoproxil fumarate nor tenofovir are substrates of CYP450 enzymes. Following IV administration of tenofovir, approximately 70% to 80% of the dose is recovered in the urine as unchanged drug within 72 hours of dosing. After multiple oral doses of tenofovir disoproxil fumarate under fed conditions, approximately 32% of the administered dose is recovered in urine over 24 hours. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.[11] Tenofovir is principally eliminated by the kidney. Dosing adjustment is recommended in all patients with creatinine clearance less than 50 ml/min. Dosage adjustments for renal impairment are available in the prescribing information. However, no safety data are available in patients with renal dysfunction who received tenofovir using these guidelines.[12]

One emtricitabine/tenofovir disoproxil fumarate tablet is bioequivalent to one emtricitabine tablet (200 mg) plus one tenofovir disoproxil fumarate tablet (300 mg) following single-dose administration to healthy adults.[13]

HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in vitro. Genotypic analysis of these isolates identified the M184I/V and K65R amino acid substitutions in viral RT.[14] Cross resistance among certain nucleoside reverse transcriptase inhibitors has been recognized. These in vitro substitutions are also observed in some HIV-1 isolates from patients failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.[15]

Adverse Events/Toxicity

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued emtricitabine or tenofovir disoproxil fumarate. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Truvada and are coinfected with hepatitis B virus (HBV) and HIV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.[16]

Immune reconstitution syndrome has been reported in some patients treated with combination antiretroviral therapy, including emtricitabine/tenofovir disoproxil fumarate. During the initial phase of combination antiretroviral therapy, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis carinii pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.[17]

Emtricitabine and tenofovir disoproxil fumarate are principally eliminated in the kidney; therefore, dosing interval adjustments of Truvada are

Emtricitabine/Tenofovir disoproxil fumarate

Adverse Events/Toxicity (cont.)

recommended for patients with decreased creatinine clearance. Truvada should not be administered to patients with low creatinine clearance or those who require hemodialysis.[18]

Drug and Food Interactions

The manufacturer recommends that Truvada not be used as a component of a triple nucleoside regimen.[19] Use of Truvada should be avoided in patients who are concurrently using or have recently used a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be monitored for changes in serum creatinine and phosphorus.[20]

Contraindications

Truvada is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product, including emtricitabine and tenofovir disoproxil fumarate.[21]

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. Truvada is not indicated for the treatment of chronic HBV infection, and the safety and efficacy of Truvada have not been established in patients coinfected with HBV and HIV.[22]

Clinical Trials

For information on clinical trials that involve Emtricitabine/Tenofovir disoproxil fumarate, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Emtricitabine/Tenofovir disoproxil fumarate AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[23]

Dosage Form: Film-coated tablets containing 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil). The recommended dose of Truvada for adults 18 years or older is one tablet once a day. Patients with lowered creatinine clearance (30 to 49 ml/min) should receive one tablet every 48 hours. Truvada should not be prescribed for patients requiring dosage adjustment, such as those with reduced renal function (creatinine clearance less than 30 ml/min or requiring hemodialysis).[24]

Storage: Store tablets at 25 C (77 F); excursions permitted to 15 C to 30 C (59 F to 86 F). Keep container tightly closed.[25]

Chemistry

CAS Name: Emtricitabine: 143491-57-0 / Tenofovir disproxil fumarate: 202138-50-9[26]

CAS Number: Emtricitabine: (2R-cis)-4-Amino-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone / Tenofovir disoproxil fumarate: Bis(hydroxymethyl) [[(R)-2(6-Amino-9H-purin-9-yl)-1-methylethoxy] methyl]phosphonate,bis(isopropyl carbonate) (ester), fumarate (1:1)[27]

Molecular formula: Emtricitabine: C8-H10-F-N3-O3-S / Tenofovir disoproxil fumarate: C19-H30-N5-O10-P.C4-H4-O4[28]

Emtricitabine: C38.86%, H4.08%, F7.68%, N17.00%, O19.41%, S12.97% / Tenofovir disoproxil fumarate: C43.47%, H5.39%, N11.02%, O35.25%, P4.87%[29]

Molecular weight: Emtricitabine: 247.24 / Tenofovir disoproxil fumarate: 635.52[30]

Melting point: Emtricitabine: 136 C to 140 C[31]

Physical Description: Emtricitabine: white to off-white crystalline powder.[32]

Tenofovir disoproxil fumarate: white to off-white crystalline powder.[33]

Solubility: Emtricitabine: 112 mg/ml in water at 25 C.[34]

Emtricitabine/Tenofovir disoproxil fumarate

Chemistry (cont.)

Tenofovir disoproxil fumarate: 13.4 mg/ml in water at 25 C.[35]

Further Reading

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Manufacturer Information

Emtricitabine/Tenofovir disoproxil fumarate
Gilead Sciences Inc
333 Lakeside Dr
Foster City, CA 94404
(800) 445-3235

Truvada
Gilead Sciences Inc
333 Lakeside Dr
Foster City, CA 94404
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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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